The effectiveness of transcutaneous tibial nerve stimulation (TTNS) for adults with overactive bladder syndrome: a systematic review

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Abstract

Aims: To evaluate effectiveness of transcutaneous tibial nerve stimulation (TTNS) for treating adults with overactive bladder (OAB) of idiopathic or neurogenic origin, using a systematic review of the literature.

Methods: Systematic searches of four databases were undertaken between 1980 and 2017. Included studies investigated effects of TTNS on OAB. Study selection, data extraction, quality appraisal was performed by two independent reviewers. Narrative analysis was undertaken where meta-analysis was not possible due to study heterogeneity. Meta-analysis of RCTs was performed using a fixed effects model.

Results: 10 RCTs and 3 prospective cohort studies involving 629 participants were reviewed. Meta-analysis of two trials comparing TTNS with sham showed mean reduction in total ICIQ Urinary Incontinence Short Form (ICIQ-UI SF) associated with TTNS of -3.79 (95% CI -5.82, -1.76; P=0.0003, I^2=25%). Narrative review showed TTNS and antimuscarinic treatment were equally effective (four trials), TTNS provided greater benefit for OAB symptoms than behavioural interventions (two trials), tibial nerve and sacral foramen stimulation were equally effective but combined stimulation was most effective (one trial). Significant improvements in OAB symptoms were reported by 48-93% participants and UI cure rates of 25-45%. No adverse events were reported.

Conclusions: Limited evidence is provided that TTNS is an effective, safe intervention for idiopathic OAB in adults and may be of benefit in those with neurogenic OAB. Further studies are essential to confirm these results as well as to determine efficacy and associated costs for specific patient groups, most effective stimulation dosage, duration of effect and stimulation regimes for longer-term maintenance.

Keywords: Transcutaneous electric nerve stimulation; tibial nerve; neuromodulation; urinary bladder, overactive.

Introduction

Overactive bladder (OAB) is an increasingly prevalent condition affecting 12-17% of the adult population[1,2] increasing to 30-40% in those aged 75 and over [3]. By 2018, it is estimated that as many as 20% of the population worldwide will suffer from OAB[4]. Although not life-limiting OAB is nevertheless life-altering and may have profound impact on a person's quality of life, ability to participate and overall wellbeing [5,6,7]. Urgency was the most commonly experienced bothersome lower urinary tract symptom (LUTS) in a large cross-sectional survey of 3727 individuals[8] and symptomatic urgency urinary incontinence (UUI) was reported as the most bothersome symptom at an individual level[8].

An algorithmic approach is taken to managing OAB, based on implementation of evidence-based recommendations arising from current research evidence. Lifestyle changes and behavioural interventions are first-line therapy in all guidance [9, 10, 11] followed by various forms of second-line pharmacotherapy, before escalating to more invasive forms of treatment such as Botox, or sacral nerve stimulation where these therapies are found to be ineffective. While lifestyle and behavioural

intervention is fundamental to managing all forms of bladder dysfunction, a significant proportion of those who go on to drug-based treatments will experience adverse effects to such a degree that they discontinue use and longer term adherence to antimuscarinic drugs is poor [12, 13]. Hence alternative, non-pharmacological approaches to long-term management of OAB are increasingly sought. The ongoing nature of OAB means that total permanent resolution is unlikely and relapsing-remitting patterns across the course of the condition have been described [14,15,16] . Such natural history and progression patterns suggest that OAB is best viewed as a 'long-term condition' which requires to be self-managed by the person, with appropriate support to do this effectively.

There is grade A evidence that electrical stimulation of the tibial nerve by inserting a 34 gauge needle (percutaneous tibial nerve stimulation (PTNS) is an effective and safe treatment for idiopathic OAB[17, 18] and the suggestion that this may also be the case for neurogenic lower urinary tract dysfunction is under investigation[19]. PTNS was first introduced in 1999[20] and has been routinely available for a number of years, receiving FDA approval in 2000 for office based treatment of OAB and approval from NICE in 2006[9]. Despite only limited understanding of its mechanisms of action it occupies an important position in the OAB treatment algorithm between low-technology lifestyle, behavioural and pharmacological interventions and intensive, invasive surgical or implanted treatments such as Botox or sacral nerve stimulation. However PTNS involves delivery of an extended programme of treatment (usually 12 sessions of 20-30 minutes duration) by trained staff in a secondary care or clinic environment and thus completion involves a significant time and travel commitment by the person with OAB. Additionally, although acknowledged as effective, the costs of the treatment programme delivery and ongoing maintenance therapy may prohibit

availability and routine use in some healthcare services and countries. Given these limitations a growing number of studies have investigated the transcutaneous route for delivering tibial nerve stimulation. This alternative non-invasive treatment is safe, using only surface electrodes and may be self-administered by the person in their own home, thus supporting self-management and avoiding travel and staff costs[21]. It is convenient because the programme of delivery is decided entirely by the person with OAB and can therefore reflect personal choices and lifestyle.

Systematic reviews of effectiveness of PTNS alone [18, 22,23,24] and general tibial nerve stimulation (including PTNS and TTNS), for OAB and urinary dysfunction[25] and for neurogenic lower urinary tract dysfunction[19] have been published. However there is no systematic review of the evidence in relation to TTNS alone. The systematic review reported here aimed to establish evidence of effectiveness of TTNS in the treatment of OAB in adult men and women.

Methods

The systematic review was carried out according to the review protocol published in PROSPERO (CRD42016041250) using Cochrane Collaboration methods and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) framework[26].

Literature search strategy

Systematic searches for published papers indexed in MEDLINE, EMBASE, CINAHL, and the Cochrane Database of Systematic Reviews between 1980 and January 2017 were undertaken using a strategy combining selected subject headings and keywords relating to TTNS, OAB, UUI, mixed UI (MUI) and study design to

determine effectiveness of the intervention. The search strategy was developed for use in Medline (Appendix 1) and amended for use in other databases. Manual searching of reference lists, relevant systematic reviews and guidelines, was also performed. Results were filtered for English language.

Selection criteria

Included study designs were randomised controlled trials (RCT) and prospective observational cohort studies and inclusion was determined by the PICO criteria: Study Participants required to be adults aged ≤ 18 years with reported subjective complaints of idiopathic or neurogenic OAB or MUI. Overactive bladder was defined according to the ICS definition as 'urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology' and mixed UI as 'the complaint of involuntary loss of urine associated with urgency and also with effort or physical exertion, or on sneezing or coughing'[27]. The intervention was TTNS, used to treat OAB or MUI. Comparators were a placebo control, another intervention, a different site of transcutaneous electrical stimulation, PTNS or TTNS as an additional intervention. Primary outcomes were self-reported symptoms of urgency, frequency, nocturia, amount of leakage or number of episodes of UI. Secondary outcomes included health-related quality of life assessed using standardised measures, adverse events reports and urodynamic changes.

Study selection

Eligible studies were selected in a two stage process. Using the broad criteria of OAB or MUI and TTNS, two reviewers (from JB, LC, SD, FD) independently screened all titles and abstracts, where available, of bibliographic records retrieved.

Full-text copies of potentially relevant studies were retrieved. Two reviewers then used the pre-determined PICO selection criteria to assess eligibility. Disagreement was resolved by discussion with a third reviewer.

Data extraction and Quality Appraisal

Two reviewers (from JB, LC, SD, FD) extracted data independently using a review-specific tool. Data extracted included details of study design and methods; study participants including sex and age; urinary symptoms, dysfunction and method of measurement; TTNS protocols, outcomes, conclusions and adverse effects. Extracted data were cross-checked and disagreements resolved by consensus. Where indicated, authors were contacted and asked to provide missing information.

Independent assessment of methodological quality was conducted for trial designs (RCTs and CCTs) using the Cochrane Risk of Bias tool[28]. Quality was assessed as being of low/unclear/high risk of bias against seven criteria: random sequence generation (selection bias), allocation concealment (selection bias), blinding of assessors (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias),and 'other'. Prospective observational cohort studies were assessed using the NICE quality assessment tool [29] to address external validity of the studies in terms of the sample representativeness within the wider population, consecutive selection of participants, clarity of aims and outcomes targeted description of findings and sample and stratification of outcomes. The maximum total score was 8.

Data analysis/synthesis

Analysis was undertaken in RevMan 5.2 [30]. For studies which reported mean differences a meta-analysis was performed to pool estimates of effect. Forest plots

were produced to visually assess the association across the included studies and the corresponding 95 % confidence intervals (CI). The chi-squared test was employed to determine strength of evidence that heterogeneity was genuine, where $P < .10$, rather than $P<.05$ was considered indicative of statistically significant heterogeneity, due to the small number of studies and sample sizes [31]. The I^2 statistic was used to quantify inconsistency, the percentage variability in effect estimates due to heterogeneity between studies rather than sampling error within studies. An I^2 value over 50% may indicate substantial heterogeneity. Pooled results were estimated using a fixed effects inverse-variance meta-analysis for difference in means between intervention and control groups with 95% CI. A fixed effect model is the best one to use when all included studies are functionally identical, there are no studies with extreme effect sizes that could influence the results and the number of studies is very small, meaning it may be difficult to estimate the between-study variance with any precision. Possibility of publication bias was evaluated by visual inspection for possible skewness in a funnel plot.

Results

Search Results

Database searches identified 1960 unique bibliographic references. Review of titles and abstracts resulted in the exclusion of 1938 papers that did not meet the broad inclusion criteria of reporting on TTNS and urge or mixed UI. Full texts were retrieved for the remaining 22 papers. These papers were screened for eligibility using the detailed PICO criteria. This resulted in the exclusion of a further 9 papers leaving 13

papers in the review (Fig. 1). Papers were rejected because they did not report on TTNS (n=8) and the full text of one paper could not be sourced.

Insert figure 1 here: Flow chart of study selection

The 13 papers reported 10 RCTs[32-41] and 3 prospective cohort studies[42,43,44]. Included studies were published between 2002 and January 2017 with 9 of the 10 trials and 2 of the 3 prospective observational studies published since 2009. Extracted data from the 13 papers are presented in the table of characteristics (Table 1)

Insert table 1 here: Study characteristics

Methodological quality of included studies

The summary of the overall risk of bias across the 10 RCTs is provided in figure 2. Risk of bias was assessed to be unclear for the majority of the trials as a consequence of inadequate reporting which was a common feature. Main sources of bias were assessed as lack of random sequence generation, poor allocation and outcomes assessment blinding and selective outcome reporting particularly in relation to attrition. The prospective observational studies were all assessed as high quality with scores of 6, 7 and 7 from a maximum of 8 using the NICE Quality Assessment Tool[29]. Two were single site studies[42, 43], one did not recruit consecutive patients[44] and one did not report stratified outcomes[42].

Insert Figure 2 - Cochrane Risk of Bias summary for 10 RCT's of TTNS here

Characteristics of studies

Overall the 13 included studies enrolled a total of 629 participants: 437 females (70%) and 176 males (28%), with 16 (2%) participants sex not reported. The 3 prospective cohort studies included a total of 157 recipients of TTNS, 41 males (26%) and 116 females (74%). The 10 RCTs enrolled a total of 472 participants, [321 women (68 %) and 135 men (32%)], of which 254 (54%) received the TTNS treatment. Thirty six participants in control groups received inactive sham (18%)[32, 33, 37],142 (56%) received anticholinergic drugs [solifenacin succinate (49, 19%)[34], oxybutynin immediate release (10, 4%)[39] and extended release (84, 33%)][35, 39] bladder training and pelvic floor muscles training (26, 10%)[38], stretching exercises (12, 5%)[36], sacral foramina transcutaneous electrical stimulation[40] or no treatment (9, 4%)[41]. Five RCTs were conducted only on women[32,35,38,39,41], one on men only[436] and 4 included mixed sex samples[33,34,37,40]. The 3 prospective cohort studies included both men and women. Participant ages encompassed the adult ages from 18 to 94, although in 10 of the 13 studies the mean age was between 45 and 69 and only one study[33] included adults over the age of 80 (table 1). Idiopathic OAB was the focus of 7 of 10 RCTs including the five women-only trials, the trial in older care home residents[33] and the trial comparing different stimulation sites[40]. Other studies focused on neurogenic OAB arising from MS[43,44], Parkinson's[37], stroke[36] and spinal cord injury[34].

Intervention: The TTNS intervention was not standardised across the studies and a range of dosages were delivered. The duration of treatment programme ranged from 4 to 12 weeks (mean 7.2 weeks, SD 3.6) and the total number of included sessions

from 5 to 90 (mean 21.6, SD 23). The length of individual stimulation sessions was 30 minutes in all but 3 studies[40,43,44] where it was 20 minutes. Timing of session delivery varied from daily stimulation in 3 studies[40,43,44], twice weekly in 7 studies[32,33,34,35,36,37,39] and once weekly in 2 studies[38,41].

Comparators: Three of the 10 RCTs compared TTNS with a sham[32,33,37], 4 trials compared TTNS with an anticholinergic drug[34,35,39,41], 1 trial compared TTNS with exercise[36], 1 trial compared TTNS as an adjunct to first-line behavioural therapy with behavioural therapy alone[38] and 1 trial compared two stimulation sites[40]. The three-arm trial reported by Souto et al[39]compared TTNS with a group receiving extended release oxybutynin alone and a group receiving TTNS in addition to the drug. Surbala et al[40] compared stimulation of the transcutaneous tibial nerve and sacral foramina sites and a combination of the two. Schreiner et al[38] compared two groups of women who underwent a first line behavioural intervention involving 12 weeks of bladder training and pelvic floor muscle training, with half also receiving 12 weeks of TTNS.

Treatment outcomes

All but one study[40] assessed clinical symptoms parameters using a voiding diary to measure primary or secondary outcomes. A range of standardised and validated patient reported symptom tools were also used including: The Overactive bladder questionnaire[45] (OABq)[32,35]; International Prostate Symptom Score[46] (IPSS)[33,41]; International Consultation on Incontinence Questionnaire – Urinary Incontinence Short Form[47] (ICIQ-UI SF)[33,37,38]; Overactive Bladder Questionnaire[48] (OAB V8)[37]; Overactive Bladder Syndrome Score[49] (OABSS)[40]; Urinary Symptom Profile[50] (USP)[43]. Quality of life measures were equally varied and included Incontinence

Quality of Life[51] (I-QoL)[34,41]; Mesure du Handicap Urinaire[52](MHU)[43,44]; Short-form Urinary Distress Inventory[53](UDI-6)[40]; Short-form Incontinence Impact Questionnaire[53](IIQ-7)[40]; Qualiveen[54] (QV)[44]. Follow up was limited in the majority of studies. Eight of the 10 RCTs measured outcomes solely at the end of the treatment period, which ranged from 4 weeks[32,34,40] to 12 weeks[35,38,39]. Two of the prospective cohort studies measured outcomes at two points: at 4 weeks[43,44], 12 weeks[44] and 10.8 months[43]. Treatment outcomes are shown in table 2. Given the heterogeneity in outcome measures used, data pooling for meta-analysis was not possible for the majority of outcomes.

Insert table 2 here – Review study outcomes

Bladder diary changes

When compared to sham, TTNS resulted in a significant reduction in urgency and nocturia in women with idiopathic OAB[32] and adults with Parkinson's [37]. Improvements in UUI were observed but not significant (Table 2). When directly compared to antimuscarinic drug treatment TTNS and extended release oxybutynin produced similar significant improvements in frequency, urgency and UUI and reduction in pad use in women with idiopathic OAB[35] (Table 2). In adults with neurogenic OAB secondary to spinal cord injury the volume per catheterisation and volume of daily leakage were reduced equally in those taking solifenacin succinate and those receiving TTNS[34]. In a comparison between lower limb stretching exercises and TTNS in men with post-stroke OAB, at six weeks and 12 months the TTNS group reported significantly improved urgency, frequency, nocturia and UUI[36]. There were no such changes found in the exercise control group; however the only statistically significant between-group differences were reported frequency at both

time-points and nocturia at 12 months[36]. Adding TTNS to standard first line behavioural interventions of bladder training and pelvic floor muscle training was effective for frequency, nocturia and urgency UI in older women with idiopathic OAB[38]. Significant improvements were shown between the TTNS-enhanced group after 12 weeks, compared to the behavioural treatment group in frequency, nocturia and episodes of urgency UI. In one RCT undertaken with older residents of care homes a significantly greater reduction in post void residual urine volume of 55ml was found in the TTNS group compared to the sham[33]. In summary, authors conclusions for voiding diary outcomes are that TTNS is effective for women with OAB[32,38], neurogenic bladder dysfunction in Parkinson's[37] and following stroke[36] and as effective as some anticholinergic drug treatment in women[35] and those with spinal cord injury[34].

OAB symptoms scores

In terms of patient-reported outcomes using standardised measures, when compared to sham intervention the IPSS scores of frail older adults treated with TTNS were significantly improved, reducing by a median of 7 points over the six-week intervention period[33]. In a group of Parkinson's patients the OAB V8 scores in those receiving TTNS improved significantly compared to the sham group where there was little change observed[37](Table 2). Comparisons between the effects of TTNS and different drugs on OAB symptoms showed that multimodal intervention (TTNS plus extended release oxybutynin) was more effective than TTNS alone over 12 and 24 weeks, however effects of TTNS were sustained over 24 weeks whereas the effects of the single drug therapy were lost[39]. The results of one small clinical controlled trial[41] suggested that TTNS was as effective as immediate-release oxybutynin but more acceptable to women with OAB. When two different stimulation

sites were compared equal effectiveness was found for reducing OAB symptoms with sacral foramina and tibial nerve sites, however a greater effect on the OABSS was produced by stimulation of both sites simultaneously[40]. Thus in summary, authors of all studies indicate TTNS to be effective for reducing reported bladder symptoms, whether compared to sham[33,37], compared to antimuscarinic drugs[39,41], with other stimulation sites[40] or over time[43,44].

Quality of Life outcomes indicated TTNS to be associated with significantly greater improvement than sham intervention on the OABq[32]. In three trials comparing TTNS and drug therapy[35,39,41] in women with idiopathic OAB, quality of life improved equally in all (Table 2). There were similar improvements in all 3 domains of the OABq with TTNS and ERO[35], however the TTNS was associated with more prolonged reductions in symptom bother than the ERO in one study [39], although combining the two resulted in the most improved quality of life. Similarly combined stimulation of sacral foramina and tibial nerve resulted in greater UDI-6 and IIQ-7 improvements than either site alone, but all were associated with significantly improved quality of life[40].

Effectiveness of TPTNS:

Variability in outcome measures and reporting (despite contacting several authors), resulted in limited opportunity to pool data in meta-analyses. However sufficient data were extracted from two studies[33,38] to enable meta-analysis of mean changes in the ICIQ-UI SF scores following a 12 session programme of TTNs. As shown in the forest plot (figure 3), compared to those in the control group meta-analysis demonstrated a clinically[55] and statistically significant mean reduction of 3.88 points

on the total ICIQ-UI SF (-5.59, -2.16; P<0.00001; I^2= 25%; 40 participants) in those who received TTNS.

Insert figure 3 here: Forest plot

Observational studies outcomes

The three prospective cohort studies reported changes in bladder function associated with use of TTNS. Ammi (2014)[43], in adults with refractory OAB and DeSeze(2011)[44] in adults with MS and refractory OAB showed daily TTNS sessions resulted in significant clinical improvements in 53% and 83% participants respectively at 30 days (table 2), which continued to 90 days in one study[44]. Improvements in standardised patient-reported measures of Mesure du Handicap Urinaire (MHU) and Urinary Symptom Profile (USP) were reported[43], together with significant improvements in urgency, frequency, number of weekly leaks and percentage of continent patients, at both 30 days and 90 days[44]. Volume at first involuntary detrusor contraction and maximum cystometric capacity were significantly increased in 50% of participants with OAB of neurogenic (n=37) or idiopathic (n=7) origin, receiving a single session of TTNS[42].

Combined outcome overall

As shown in table 2, results from 9 studies report significant improvement in LUTS in 48% to 93% of participants undergoing TTNS intervention[32,33,35,36,38,39,41,43,44]. Cure rates of 25% to 45% for UI were reported in three studies[35,36,44].

No adverse events were reported by any study reporting use of TTNS.

Discussion

Our systematic review of 10 RCTS and 3 prospective cohort studies involving 629 participants indicates that 48-93% participants achieved significant symptom improvement following a programme of TTNS. Meta-analysis of data from two studies found a clinically and statistically significant reduction of 3.88 points on the ICIQ-UI SF, indicating that TTNS is an effective, non-invasive treatment for OAB in older adults. Additionally the absence of any reports of stimulation-related adverse events in the review confirmed the safety and tolerability of TTNS across adult populations for both idiopathic and neurogenic OAB.

Despite these promising findings there are a number of factors which suggest the need for caution in interpreting the review results. The studies were generally small, only two of the RCTs recruited according to a power calculation[35,39] and risk of bias in the RCTs was unclear or high for the majority. Heterogeneity was marked in relation to participants' age, sex, medical and urological conditions with a mix of idiopathic and neurogenic bladder dysfunction of variable duration and a tendency for more moderate than severe OAB symptoms represented.

The TTNS intervention was not standardised and the dose delivered varied between studies, although all used low frequency stimulation of 10-20 Hz. In terms of hours of stimulation this ranged between 2.5 hours and 12 hours in the RCTs and 10 and 30 hours in the prospective observational studies, showing the wide variation. Currently there is no evidence of superior efficacy with longer duration of stimulation and the optimum intervention programme or duration has not yet been established. A study using percutaneous tibial nerve stimulation suggests more frequent stimulation leads to a more rapid response however there was no difference between weekly and three times weekly dosages with regard to overall treatment outcome[57]. Primary and secondary outcomes measured were varied and included individual LUTS, different

types of UI, changes in quality of life and urodynamic parameters. Eleven validated tools were used to measure outcomes across 13 studies. Due to differences in reporting of data, where some studies reported mean results and others mean changes and the lack of response from authors contacted to provide further information, data pooling was not possible for most reported outcomes. There was a lack of long-term follow up beyond 12 weeks; one trial reported outcomes at 6 months[39] and one at 12 months[36] and one prospective observational study followed women for a mean of 10.8 months[43]. Thus duration of potential effect is unclear and should be investigated in future research.

Economic evaluation was not formally addressed in any of the included studies; however Manriques (2016)[35] discussed the affordability of TTNS stating a one-off cost of 45 euros for the TTNS equipment compared to a monthly average cost of antimuscarinics of 50 euros. Recent audit has shown costs associated with TTNS to be considerably lower than three routinely used anticholinergics in the UK at 2015 costs[58]. Nevertheless there is a lack of information on long-term economic aspects and comparison with other therapies, such as percutaneous TNS. Such information is required before implications for future practice can be reliably considered.

An important clinical issue is the place of TTNS in the OAB treatment algorithm. This review indicates the potential effectiveness of TTNS for use in idiopathic OAB and its safety for treating neurogenic OAB. These findings, together with the utility of TTNS in a supported self-management regimen[22,25] and the low cost of the intervention[58] make TTNS an attractive option for inclusion earlier in the treatment algorithm. Schreiner (2010)[38] recommended that it is included as first line conservative therapy as an adjunct to lifestyle and behavioural conservative management in older women with UUI. Given its safety and the passive nature of the intervention there is also

potential for application in clinical situations where behavioural, lifestyle and pharmacological therapies might be inappropriate or contra-indicated, such as in the older, cognitively impaired population.

Previous systematic reviews have combined percutaneous (needle-electrode) TNS and transcutaneous (surface electrode) TNS in the same review[19,23,56], hence the current lack of clarity in our understanding of effectiveness, cost-effectiveness and best position in the treatment algorithm for each intervention and the tendency to consider them as equivalent. This situation fails to recognise the potential to target each more carefully. While the possibility of equal effectiveness for the two routes of administration is accepted, it is also conceivable that there are differing mechanisms of action associated with each, which have yet to be identified. Our review results for TTNS suggest similar success rates to those achieved in the PTNS studies. Given the current lack of reliable information, all reviews of TNS regardless of type, highlight the need for greater information, particularly in terms of identifying predictors of those who will respond to treatment and likely success rates.

Conclusion

All studies in this systematic review demonstrate some benefit from TTNS, in terms of patient reported and urodynamic parameters. Safety and tolerability of the intervention is confirmed. However, in view of the limited quality of evidence further research is necessary to confirm effectiveness for specific patient sub-groups, as well the magnitude of effect sizes associated with use of TTNS for treating OAB in adults, the optimal stimulation programme, potential sustainability and duration of effect. The place of the transcutaneous route of delivery in the treatment algorithm, in contrast to the more costly and labour-demanding percutaneous route has yet to

be clarified, particularly in relation to the promising role for TTNS in ongoing self-management of OAB. Nevertheless, given its safety, low cost, ease of application and potential to support self-administration, there is a clear impetus for further research to establish definitive evidence on the role of TTNS as second-line therapy, after lifestyle and behavioural changes have been implemented and as a direct alternative to pharmacological therapy in adults with OAB of idiopathic or neurogenic aetiology.

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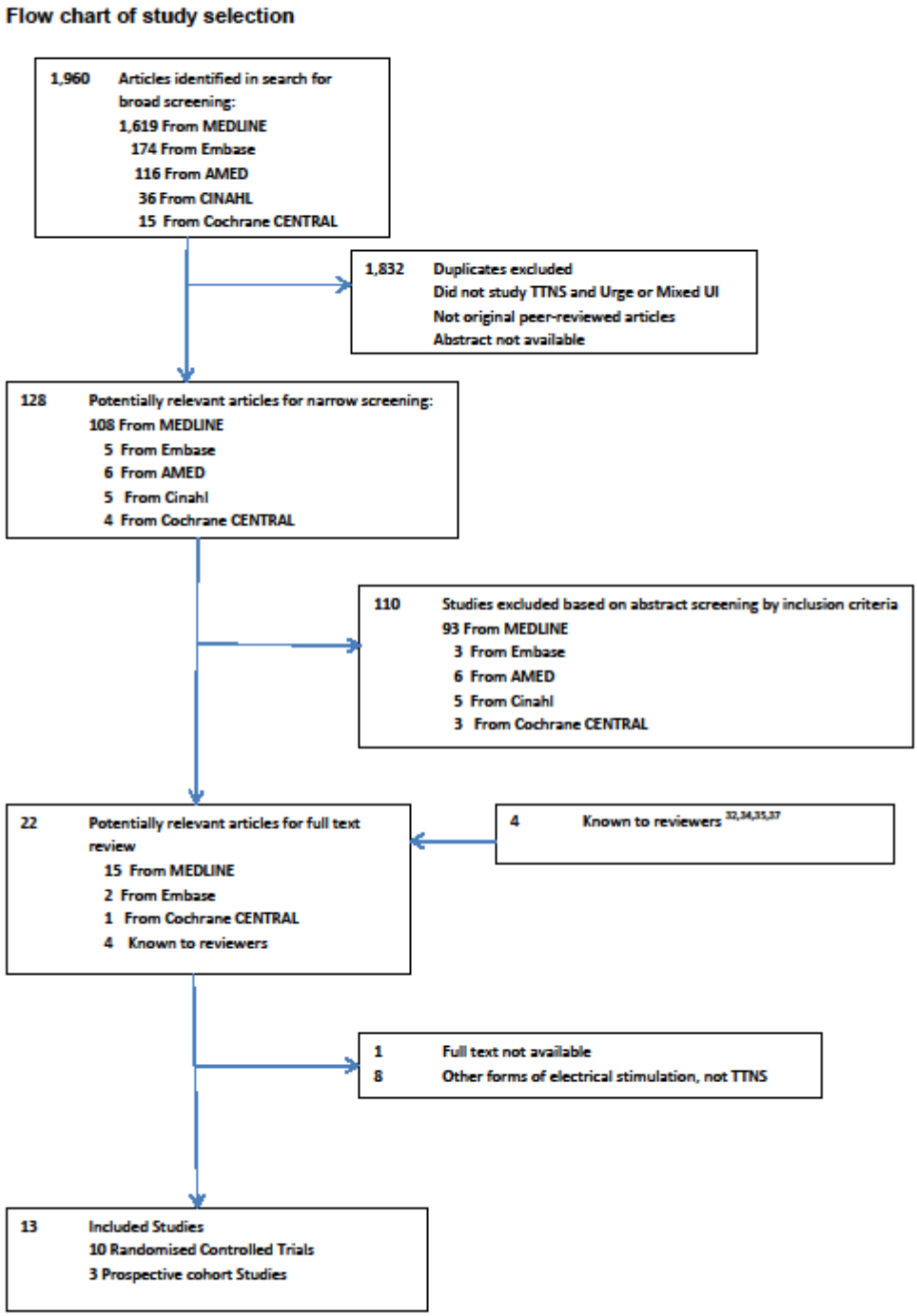
Figure 1 – Flowchart of study selection



Study	Total number patients	Mean age (SD), (SE) [range]	Type of OAB/ MUI	Participants (female/male)	Type of stimulation +/or treatment	Stim freq (Hz)	Pulse width (μS)	Stim session duration (mins)	Intensity (mA)	Total number sessions	Stim programme duration (weeks)	Outcomes measured
RCTs												
Bellette, 2009	37	47.7 (10.9)	Idiopathic	Int 21 (21/0) Con 16 (16/0)	TTNS Sham	10	200	30	NR	8	4	72 hour bladder diary, OABq
Booth, 2013 UK	30	84.2 (10.0)	Idiopathic neurogenic	Int 15 (12/3) Con 15 (12/3)	TTNS Sham	10	200	30	Sensory/or motor threshold	12	6	AUASI, ICIQ-UI SF, PVRUV
Chen, 2015	100	32.9 (1.8) 33.5 (1.7)	Neurogenic	Int 49 (3/46) Con 48 (3/ 45)	TTNS SS 5mg daily	20	200	30	Highest tolerated	8	4	72 hour bladder diaries, I-QoL
Manriques, 2016	70	54.5 [18-84] 53.0 [18-71]	Idiopathic	Int 36 (36/0) Con 34 (34/0)	TTNS ERO 10mg daily	20	200	30	Motor threshold	24	12	72 hour bladder diary, OABq
Monteiro, 2014	24	65.1 (3.6) 56.1 (10.9)	Neurogenic	Int 12 (0/12) Con 12 (0/12)	TTNS Leg stretching exercises	10	200	30	Motor threshold	12	6	72 hour bladder diary
Perisinotto 2015	13	63.5 [51-80] 57.0 [50-68]	Neurogenic	Int 8 Con 5	TTNS Sham	10	200	30	Sensory threshold	10	5	72 hour bladder diary, OAB V8, ICIQ-UI SF
Schreiner, 2010	51	68.3 (5.3) 67.6 (5.2)	Idiopathic	Int 25 (25/0) Con 26 (26/0)	BT,PFME, TTNS BT, PFME	10	200	30	Sensory / or motor threshold	12	12	72 hour bladder diary, ICIQ-UI SF
Souto 2014	75	56.9 [33-71] 57.7 [34-79] 60.1 [33-77]	Idiopathic	Int 25 (25/0) Con 1 25 (25/0) Con 2 25 (25/0)	TTNS ERO 10mg daily TTNS + ERO	10	250	30	Highest intensity tolerated	24	12	ICIQ-UI SF, ICIQ-OAB, 72 hour bladder diary
Surbala 2014	44	43.6 [7.56] 42.8 [8.12] 47.2 [8.83]	Idiopathic	Cont 15 (10/5) Int 1 15 (9/6) Int 2 14 (11/3)	SF TTNS SF+TTNS	10	200	20	Highest intensity tolerated	24	4	OABSS, UDI-6, IIQ-7
Svihra, 2002	28	54 [45-63]	Idiopathic	Int 9 (9/0) Con 1 10 (10/0) Con 2 9 (9/0)	TTNS IRO 15mg No treatment	1	100	30	25	5	5	IPSS, I-QOL
Prospective observational studies												
Amarenco 2003	44	53.3 (18.2)	Neurogenic Idiopathic	29 / 15	TTNS	10	200	NA	Motor threshold	NA	NA	First IVD, MCC
Ammi, 2014	43	61.2 (15.7)	Refractory Idiopathic Neurogenic	36 / 7	TTNS	10	200	20	Discomfort threshold	30	4	USP, MHU
De Seze, 2011	70	48.3 (10.2)	Neurogenic.	51 / 19	TTNS	10	200	20	Perception threshold before pain.	30 90	4 12	72 hour bladder diary, MHU, WT, Qualiveen

Key: OAB = Overactive bladder; MUI = Mixed Urinary Incontinence; OABq = Overactive bladder questionnaire; AUASI = American Urological Association Symptom Index; ICIQ_UI SF = International Consultation on Incontinence Questionnaire – Urinary Incontinence Short Form; PVRUV= Post Void Residual Urine Volume; I-QOL = Incontinence Quality of Life; SS = solifenacin succinate; ERO = Extended Release Oxybutynin; BT = Bladder Training; PFME = Pelvic Floor Muscle Exercises; NR = Not reported; IRO=Immediate Release Oxybutynin; IPSS = International Prostate Symptom Score; MHU = Mesure du Handicap Urinaire; WT = time between perception of the strong desire to void and leakage; OABSS = Overactive Bladder Syndrome Score; UDI-6 = Short-form Urinary Distress Inventory -6 item score; IIQ-7 = Short-form Incontinence Impact Questionnaire – 7 item score; USP=Urinary Symptom Profile; IVD = Involuntary detrusor contraction; MCC- maximum cystometric capacity

Table 1 – Characteristics of included studies

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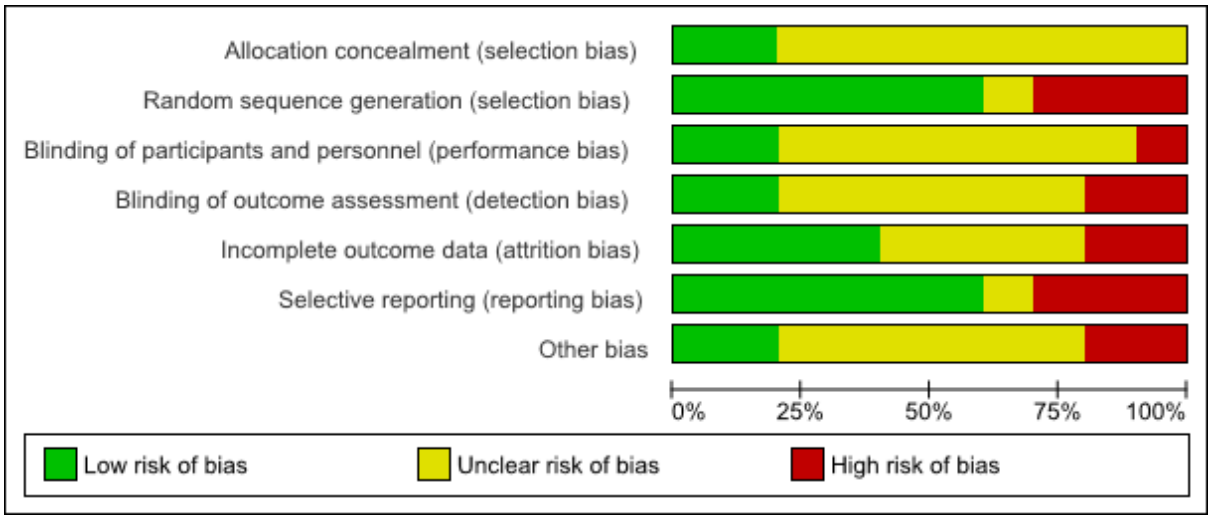

Figure 2 – Cochrane Risk of Bias summary

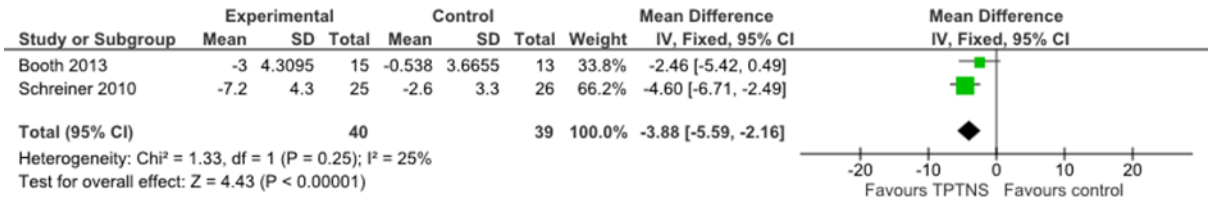

Figure 3 – Forest plot – effects of TTNS on ICIQ-UI SF scores

Study	Bladder diary outcomes			Standardised symptom scores				Quality of life				Authors conclusions
TTNS versus Sham stimulation												
Bellette 2009	TTNS % with urgency 0 wk 91 4 wk 43 P=.002 Frequency/24 hrs 0 wk 11.4 4 wk 8.3 P=.003 Nocturia 0 wk 2.4 4 wk 1.1 P=.001	Sham % with urgency 0 wk 94 4 wk 63 P =.025 Frequency/24 hrs 0 wk 13.9 4 wk 10.6 Nocturia 0 wk 2.6 4 wk 2.1	BtwG P=.009 P=.054 P=.018					TTNS Severity OABq (SD) 0 wk 68.6 (18.9) 4 wk 31.7 (18.3) P<.001 Total OABq 0 wk 52.3 (18.6) 4 wk 84.0 (17.0) P<.001	Sham Severity OABq (SD) 0 wk 67.5 (20.7) 4 wk 51.2(32.1) P<.001 Total OABq 0 wk 50.9 (17.4) 4 wk 66.6 (25.1) P<.001	BtwG P=.018 P=.037	TTNS is an effective treatment for OAB in women and improves quality of life
Booth 2013	TTNS Mean change (SD) PVR urine volume 60ml (80ml)	Sham Mean change (SD) PVR urine volume 4.8ml (23ml)	P=.048	TTNS 6 wk median change AUASI score (IQR) -7 (-8 to -3) 6 wk median change ICIQUI SF (IQR) 2 (-6 to 0) 87% LUTS improved	Sham 6 wk median change AUASI score (IQR) 1 (-1 to 4) 6 wk median change ICIQUI SF (IQR) 0 (-3 to 3)	P<.001 P=.132						Evidence of potential reduction in LUTS Potential TTNS reduces PVR urine volume
Perisinotto 2015	TTNS 72 hour urgency 0 wk 8 10 wk 1 P<.04 72 hour UUI 0 wk 6 10 wk 4 Nocturia 0 wk 4 (2-6) 10 wk 2 (0-12) P <.01	Sham 72 hour urgency 0 wk 5 10 wk 5 72 hour UUI 0 wk 3 10 wk 3 Nocturia 0 wk 4 (0-5) 10 wk 4 (0-5)	 P=.82	TTNS OAB V8 0 wk 18 (6-27) 10 wk 16 (6-25) P<.03	Exercise control OAB V 8 0 wk 29 (11-33) 10 wk 21.5 (6-21.5) P=.58	P = .10					Findings suggest TTNS is effective in treatment of LUTS in people with Parkinson's
TTNS vs drug intervention												
Chen 2015	TTNS VPC (ml + SD) 0 wk 258.7 ± 14.7 2 wk 282.5 ± 15.2 P<.05 4 wk 294.1 + 15.4 Vol leak/day (ml + SD) 0 wk 766.4 + 61.5 2 wk 563.3+45.4 P<.05 4 wk 541.4 +47.5	SS VPC (ml + SD) 0 wk 243.1 + 15.8 2 wk 302.6+ 23.3 P<.05 4 wk 301.3 + 21.1 Vol leak/day (ml + SD) 0 wk 753.9 +121.7 2 wk 444.1+87.1 P<.05 4 wk 449.1 + 89.2	 NS NS					TTNS I-QOL (SD) 0 wk 9.5 + 0.7 2 wk 25.1 + 1.2 P<.05 4 wk 25.2 + 1.0	SS I-QOL (SD) 0 wk 9.1 + 0.8 2 wk 24.0 + 0.9 P<.05 4 wk 24.2 + 1.0	NS	Similar results were achieved with TTNS and SS for bladder diary and QoL outcomes
Manriques 2016	TTNS 72 hr Frequency 0 wk 24 (12-48) 12 wk 18 (11-54) P=.0035 72 hr Urgency 0 wk 14 (0–49) 12 wk 5 (0–15) P<.001 72 hr UUI 0 wk 5 (0–24) 12 wk 0 (0–30) P=.001 Daily pads 0 wk 7 (0–19) 12 wk 2 (0–30) P=.0022 70% successful treatment response (>50% reduced frequency). 25% achieved dryness	ERO 72 hr Frequency 0 wk 28 (11–55) 12 wk 20.5 (9–44) P= .001 72 hr Urgency 0 wk 16 (4–47) 12 wk 4.5 (0–27) P=.0004 72 hr UUI 0 wk 4 (0–22) 12 wk 0 (0–27) P=.0005 Daily pads 0 wk 9 (0–36) 12 wk 0 (0–30) P=.001 60% successful treatment response 13% achieved dryness	P=.400 P=.490 P=.232 P=.767					TTNS OABq domain 1 0 wk 33 (30–35) 12 wk 16 (10–46) P<.001 OABq domain 2 0 wk 55 (49–60) 12 wk 30 (15–83) P<.001 OABq domain 3 0 wk 35 (31–39) 12 wk 20 (10–51) P<.001	ERO OABq domain 1 0 wk 33 (31–36) 12 wk 18 (8–45) P=.0004 OABq domain 2 0 wk 60 (54–66) 12 wk 37 (17–79) P=.0002 OABq domain 3 0 wk 36 (32–40) 12 wk 23 (11–57) P=.0281	P=.886 P=.036 P=.136	Similar improvements in women with OAB were demonstrated with TTNS and ERO
Souto 2014				TTNS ICIQUI SF 0 wk 16.3 (0-21) 12 wk 7.2 (0-18) 24 wk 8.3 (0-20) ICIQ-OAB 0 wk 10.3 (7-15) 12 wk 5.9 (1-11) 24 wk 6.1 (1-12) 12 wk 83% report no UI	ERO ICIQ-SF 0 wk 17.1 (0-21) 12 wk 9.8 (0-18) 24 wk 13.3 (8-20) ICIQ-OAB 0 wk 1.8 (8-16) 12 wk 4.6 (0-10) 24 wk 9.2 (4-13) 12wk 69% report no UI	Multimodal ICIQUI SF 0 wk 16.9 (0-21) 12 wk 7.9 (0-14) 24 wk 7.4 (0-14) ICIQ-OAB 0 wk 11.0 (7-16) 12 wk 2.9 (0-5) 24 wk 3.0 (0-5) 12 wk 76% report no UI	P=.88 P=.31 P=.0006 P=.15 P=.01 P=.0001	TTNS Bother 0 wk 8.3 (8-10) 12 wk 3.9 (0-8) 24 wk 4.2 (0-8)	ERO 0 wk 8.4 (4-10) 12 wk 3.4 (0-9) 24 wk 7.0 (2-10)	Multimodal 0 wk 8.3 (4-11) 12 wk 1.7 (0-4) 24 wk 1.6 (0-4)	P=.92 P=.06 P=.001	Multimodal treatment was more effective. TTNS (alone, or in association) presented longer lasting results for OAB than ERO
Svhira 2002				TTNS With >50% improvement, 5 (56%) improved 2 (22%) NS improvement 2 (22%) no response Mean IPSS (SD) 0 wk 17 (3) 5 wk 6 (4)	Oxybutynin Comparable therapeutic results. 2 (20%) refused further treatment	Control No significant changes		TTNS Mean I-QOL (SD) 0 wk 36 (10) 5 wk 68 (20)	Oxybutynin NR	Control NR		TPTNS improved subjective OAB symptoms, had no adverse effects and was well tolerated
TTNS vs behavioural intervention												
Monteiro 2014	TTNS Urgency* 0 wk 11 (92%) 6 wk 7(58%) P<.05 12 mth 6 (50%) P=.02 UUI 0 wk 11 (92%) 6 wk 8(67%) P=.13 12 mth 7 (58%) P=.05 Frequency 0 wk 0 (83%) 6 wk 3(25%) P=.004 12 mth 0(0%) P=<.01 Nocturia 0 wk 10 (83%) 6 wk 5(42%) P=.03 12 mth 1 (8%) P=. 0002	Exercise control Urgency* 0 wk 10 (83%) 6 wk 10 (83%) 12 mth 9 (75%) UUI 0 wk 9 (75%) 6 wk 9 (75%) 12 mth 8 (67%) Frequency 0 wk 11 (92%) 6 wk 11 (92%) 12 mth 9 (75%) Nocturia 0 wk 9 (75%) 6 wk 9 (75%) 12 mth 6 (50%)	 P=.18 P=.20 P=.65 P=.67 P<.001 P<.001 P=.09 P=.02									TTNS is a safe and effective option for treatment of post stroke neurogenic OAB in men
Schreiner 2010	TTNS Mean frequency (SD) 0 wk 7.2 (2.3) 12 wk 5.9 (1.4) P=.003 Mean nocturia (SD) 0 wk 2.9 (1.8) 12 wk 1.3 (1.5) P<.001 UUI episodes/72 hrs 0 wk 8.1 (5.2) 12 wk 1.8 (2.7) P<.001	BT & PFME Control Mean frequency (SD) 0 wk 7.0 (2.0) 12 wk 6.8 (1.9) P=.306 Mean nocturia (SD) 0 wk 2.4 (1.3) 12 wk 2.0 (1.4) P=.061 UUI episodes/72 hrs 0 wk 5.8 (3.0) 12 wk 4.6 (3.7) P<.001	P=.647 P=.013 P=.191 P<.001 P=.072 P<.001									TTNS is efficacious to treat urge UI in older women. It can be used as initial therapy in association with PFME and BT
TTNS vs other stimulation site												
Surbala 2014				TTNS OABSS Pre 10.8±2.1 Post 6.8±2.3 P<.000	SF OABSS Pre 10.6±2.1 Post 6.0±1.8 P<.000	TTNS plus SF OABSS Pre 10.9±2.1 Post 4.8±2.1 P<.000	P=.042	TTNS UDI-6 Pre 14.6 ± 1.9 Post 8.1±2.3 IIQ-7 Pre 15.9 ±1.9 Post 8.1±1.7 P<.000	SF UDI-6 Pre 14.7±2.0 Post 7.1±1.9 IIQ-7 Pre 16.3±1.8 Post 7.5±2.2 P<.000	TTNS plus SF UDI-6 Pre 14.9±2.1 Post 5.9±2.7 IIQ-7 Pre 17.2±1.5 Post 6.0±2.7 P<.000	P=.048 P=.038	Stimulation at both sites reduced OAB symptoms. Simultaneous stimulation at SF+PTN was more effective than single site stimulation. Stimulation at all sites improved QoL
Cohort studies												
Amarenco 2003	Mean FIDC on standard cystometry 162.9±96.4ml With TTNS 232.1 + 115.3ml Mean MCC on standard cystometry 221±129.5ml With TTNS 277.4 ± 117.9ml Positive test if FIDC and/or MCC volume increased by 100ml or 50% during standard cystometry Test positive in 22 of 44 subjects with TTNS		P<0.0001 P<0.0001									Results suggest an objective acute effect of TPTNS on urodynamic parameters
Ammi 2014	TTNS successful after 1 month in 53% (23/43). Mean follow-up 10.8 ± 1.6 months: 49% (21/43) continued TTNS			Mean USP from 14 ±3.3 to 6.9 ± 3.2 Follow up USP scores 5.4 ± 3.5 Remained lower than baseline			P<.001 P<.001	Mean MHU from 11.8 ±2.8 to 5.6 ± 3 Follow-up MHU scores 4.4 ± 2.8 Remained lower than baseline			P<.001 P<.001	TTNS is well tolerated and effective in half of patients with failed drug treatment
De Seze 2011	Severe Urgency 0 days 51% 30 days 19% 90 days 24% Urgency, min (warning time) 0 days 8.5 (10.5) 30 days 11.6 (13.4) 90 days 13.3 (15.0) Frequency 0 days 11.3 (5.5) 30 days 8.6 (4.3) 90 days 8.9 (4.3) Leakage per week 0 days 5.8 (9.4) 30 days 2.8 (5.4) 90 days 3.1 (6.4) % continent patients 0 days 25.7% 30 days 45% 90 days 47%		 P<.001 P<.001 P<.001 P<.001 P<.001 P<.001 P<.001 P=.002 P=.005 P=.005									Continued TTNS appears to be effective in the management of severe OAB in MS, without compromising bladder emptying or inducing side effects

Table 2. – Review study outcomes

Table 2 – Review study outcomes

Key: I = Intervention; C = Comparison; TTNS = Transcutaneous Tibial Nerve Stimulation; OAB = overactive bladder; BD = bladder diary; UUI = urge urinary incontinence; AUASI = American urological Association Symptom Index; ICIQUI-SF = International Consultation on Incontinence Questionnaire Urinary Incontinence Short Form; LUTS = Lower Urinary Tract Symptoms; OABV8 = Overactive Bladder Awareness Tool; NDO=Neurogenic Detrusor Overactivity; ERO = Extended Release Oxybutynin; IPSS = International Prostate Symptom Score; SF = Sacral Foramina Stimulation; OABSS = Overactive Bladder Symptom Score, GRA = Global Response Assessment; OABq = Overactive Bladder Questionnaire, SF-36= 36-Item Short Form Health Survey; PVR = post-void residual urine volume; SS = solifenacin succinate; VPC = Volume Per Catheterisation; BT = Bladder Training; PFME = Pelvic Floor Muscle Exercises; ERO = Extended Release Oxybutynin; UDS = urodynamic studies; DI = Detrusor Instability; USP=Urinary Symptom Profile; MHU = Mesure du Handicap Urinaire; NOUR = non-obstructive urinary retention; GRA = Global Response Assessment; FIDC = First Involuntary Detrusor Contraction; MCC= Maximum Cystometric Capacity; OR = odds ratio; CI = confidence interval; NS = Not significant.